EXHIBIT A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 204152

ANDA APPROVAL

Perrigo R&D Company
515 Eastern Avenue
Allegan, MI 49010
Attention: James Chambers
Senior Manager-Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 29, 2012, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), for Omeprazole Magnesium Delayed-release Tablets, 20.6 mg (20 mg base).

Reference is also made to the Complete Response letter issued by this office on December 31, 2014, and to your amendments dated June 29 and July 20, 2015.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. **Accordingly the ANDA is approved**, effective on the date of this letter. The Division of Bioequivalence has determined your Omeprazole Magnesium Delayed-release Tablets, 20.6 mg, to be bioequivalent to the reference listed drug (RLD), Prilosec OTC Delayed-release Tablets, 20.6 mg, of AstraZeneca Pharmaceutical Company (AstraZeneca).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted in:

Buffer stage:

Medium:	Tablets are pre-exposed to 300 mL of 0.1 N HCl for 2 hours and then 700 mL of 0.086 M Na_2HPO_4 is added to the medium containing the tablets to give 1000 ml with pH 6.8.
Apparatus:	USP Apparatus II (paddle)
Speed:	100 rpm

(b) (4)

(b) (4)

Specifications:

NMT (b) (4) (Q) of Omeprazole in the dosage form is dissolved in 120 min

NLT (b) (4) (Q) of Omeprazole in the dosage form is dissolved in 30 min

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement – Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, AstraZeneca's Prilosec OTC Delayed-release Tablets, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

U.S. Patent Number	Expiration Date
5,817,338 (the '338 patent)	October 6, 2015
5,900,424 (the '424 patent)	May 4, 2016
6,403,616 (the '616 patent)	November 15, 2019
6,428,810 (the '810 patent)	November 3, 2019

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Omeprazole Magnesium Delayed-release Tablets, 20.6 mg, under this ANDA. You have notified the agency that Perrigo R&D Company (Perrigo) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that no action for infringement was brought against Perrigo within the statutory 45-day period.

With respect to 180-day generic drug exclusivity, we note that Perrigo was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Perrigo is eligible for 180 days of generic drug exclusivity for Omeprazole Magnesium Delayed-release Tablets, 20.6 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

You have been requested to provide information after the ANDA has been approved. Any information submitted to meet the conditions requested in this letter is considered a "Post Approval Commitment Response." To alert the Office of Generic Drug staff to the fact that you are providing post approval commitment information, please designate your submission in your cover letter as "POST APPROVAL COMMITMENT RESPONSE."

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

William P. Rickman -S

Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300043242, cn=William P. Rickman -S
Date: 2015.07.30 10:26:43 -04'00'

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

EXHIBIT B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206877

TENTATIVE APPROVAL

Aurobindo Pharma USA, Inc.
U.S. Agent for Aurobindo Pharma Limited
2400 Route 130 North
Dayton, NJ 08810
Attention: Ms. Blessy Johns

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) for Omeprazole Delayed-Release Tablets, 20 mg (OTC).

Reference is made to your amendments dated May 29, and July 22, 2014; May 5, and August 27, 2015; and January 14, February 4, and March 25, 2016.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Prilosec OTC Delayed-Release Tablets, 20 mg of AstraZeneca Pharmaceuticals LP, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 6,403,616 (the '616 patent) and 6,428,810 (the '810 patent) are scheduled to expire on November 15, 2019 and November 3, 2019, respectively.

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Omeprazole Delayed-Release Tablets, 20 mg (OTC), under this ANDA. You have notified the agency that Aurobindo Pharma Limited (Aurobindo) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that no action for infringement was brought against Aurobindo within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

However, we are unable at this time to grant final approval to your ANDA. Prior to the submission of your ANDA, another applicant or applicants submitted a substantially complete ANDA providing for Omeprazole Delayed-Release Tablets, 20 mg (OTC) and containing a paragraph IV certification. Your ANDA will be eligible for final approval on the date that is 180 days after the commercial marketing date identified in section 505(j)(5)(B)(iv) of the FD&C Act.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMPs are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the FD&C Act, and will not be listed in the "Orange Book."

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those

responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Mr. Ashley Burns, Regulatory Project Manager, at (240) 402-7111 or ashley.burns@fda.hhs.gov.

Sincerely yours,

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

EXHIBIT C

US006403616B1

(12) **United States Patent**
Erickson et al.

(10) **Patent No.: US 6,403,616 B1**
(45) **Date of Patent: Jun. 11, 2002**

(54) **CHEMICAL PROCESS AND PHARMACEUTICAL FORMULATION**

(75) Inventors: **Magnus Erickson**, Västra Frölunda; **Anders Gustavsson**, Nykvarn; **Lars Josefsson**, Sävedalen, all of (SE)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/485,897**

(22) PCT Filed: **Nov. 15, 1999**

(86) PCT No.: **PCT/SE99/02093**

§ 371 (c)(1),
(2), (4) Date: **Feb. 17, 2000**

(87) PCT Pub. No.: **WO00/28975**

PCT Pub. Date: **May 25, 2000**

(30) **Foreign Application Priority Data**

Nov. 18, 1998 (SE) 9803952
Nov. 18, 1998 (SE) 9803953

(51) **Int. Cl.**[7] **A61K 31/44**; C07D 401/12; C07D 235/28; C07D 471/04

(52) **U.S. Cl.** **514/338**; 514/303; 514/393; 514/395; 546/118; 546/273.7; 548/303.7; 548/306.4

(58) **Field of Search** 546/273.7, 118; 548/306.4, 303.7; 515/303, 338, 395, 393

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

EP	0519144	12/1992
WO	8602646	5/1986
WO	9427988	12/1994
WO	9501783	1/1995
WO	9501977	1/1995
WO	9532959	12/1995
WO	9601624	1/1996
WO	9601625	1/1996
WO	9702020	1/1997
WO	9741114	11/1997

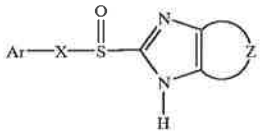
OTHER PUBLICATIONS

Pilbrant and Cederberg, Development of an oral formulation of omeprazole, Scand. J. Gastroenterology, 1985; 20 (suppl. 108) pp. 113–120, Molndal, Sweden.

Primary Examiner—Bernard Dentz
(74) *Attorney, Agent, or Firm*—White & Case LLP

(57) **ABSTRACT**

Process for the manufacturing of slightly soluble or less soluble alkaline salts of substituted sulphinyl heterocycles containing an imidazole moiety with formula I

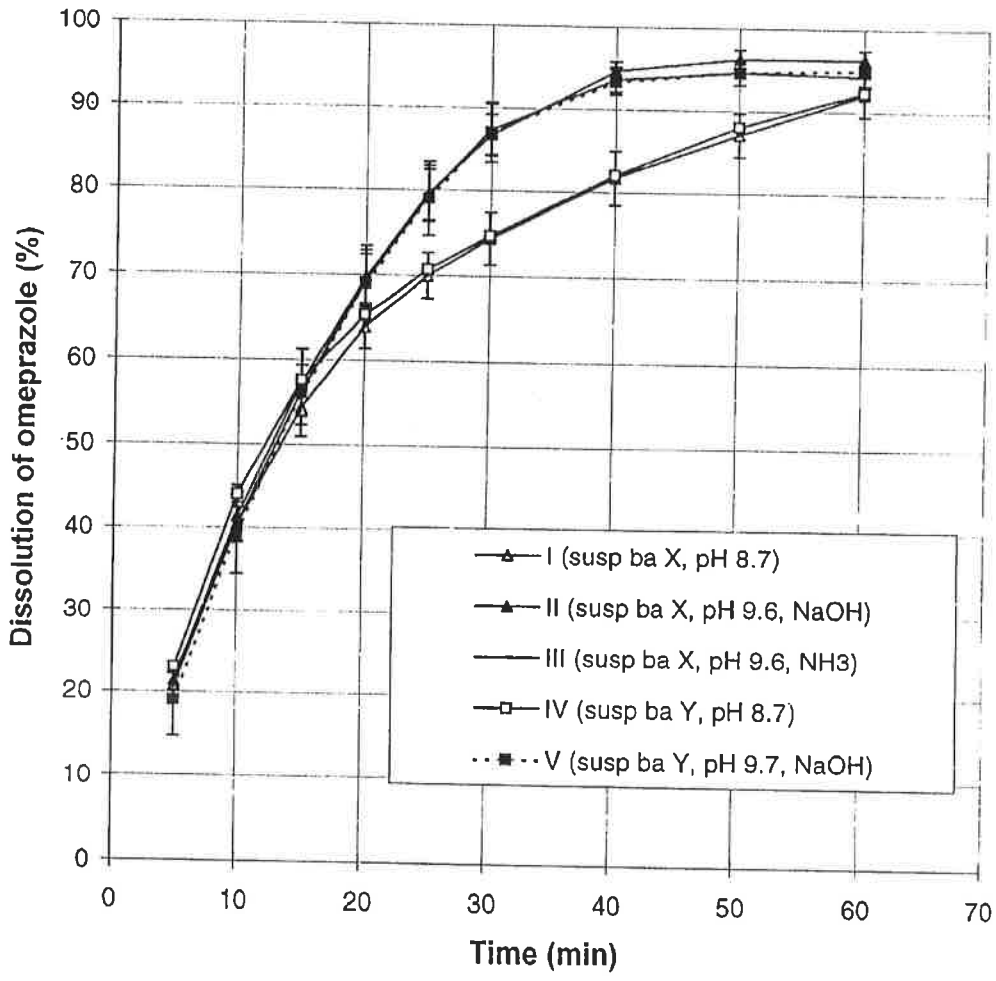


I

preferably alkaline salts of a proton pump inhibitor compound, wherein the process comprises the step of reacting the substituted sulphinyl heterocycle of Formula I with a source of the cation in the presence of a base, characterized by a washing step in which the prepared alkaline salt of the substituted sulphinyl compound is washed with a basic aqueous solvent mixture. The obtained bulk drug substance resulting in a bulk product that in an aqueous suspension of the substituted sulphinyl heterocycle having a pH not significantly lower than that of a saturated water solution of the pure compound prepared. Alternatively, the process for manufacturing a pharmaceutical dosage form comprising the active substance could be adjusted. For instance the pH of an aqueous suspension of the active substance is adjusted to a pH not significantly lower than that of a saturated water solution of the pure compound. The processes are preferably useful in the manufacturing of omeprazole magnesium salt or magnesium salt of one of its single enantiomers used in pharmaceutical dosage forms.

18 Claims, 1 Drawing Sheet

Fig. 1


Dissolution of omeprazole (%)
Time (min)
0
10
20
30
40
50
60
70
80
90
100
I (susp ba X, pH 8.7)
II (susp ba X, pH 9.6, NaOH)
III (susp ba X, pH 9.6, NH3)
IV (susp ba Y, pH 8.7)
V (susp ba Y, pH 9.7, NaOH)

CHEMICAL PROCESS AND PHARMACEUTICAL FORMULATION

This application is a 371 of PCT/SE99/02093 filed Nov. 15, 1999.

FIELD OF THE INVENTION

The present invention relates to an improved process for the manufacturing of an alkaline salt of an acid susceptible proton pump inhibitor compound, such as a substituted sulphinyl heterocyclic compound containing an imidazole moiety. More specifically the invention is related to an improved process for the manufacturing of an alkaline salt of omeprazole or an alkaline salt of (S)-omeprazole, preferably magnesium salts of these compounds. The invention is also related to an improvement in the preparation of the pharmaceutical formulation and to products containing as the active ingredient a compound prepared by the claimed processes as well as the use of the products in medicine.

BACKGROUND OF THE INVENTION AND PRIOR ART

Substituted benzimidazoles such as for instance the compounds with the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole have properties making the compounds useful as inhibitors of gastric acid secretion. This class of compounds is known as proton pump inhibitors or H^+,K^+-ATPase inhibitors. There are a large number of patents and patent applications disclosing such proton pump inhibitors and processes for their manufacturing.

There is a general need in industry that pharmaceutically active compounds should be produced by processes giving products with properties, such as being easy to handle in full scale manufacturing and having good stability during storage, making them suitable for pharmaceutical preparations. The active substance, the drug, should also be presented in a form with such physico-chemical properties that are suitable for pharmaceutical manufacturing processing, and the drug should be released from the dosage form with a rate suitable for its intended pharmacological effect. Usually, it is the concern of the formulator to develop dosage forms with the desired properties. However, to obtain a good formulation, it is beneficial and important that the active substance as such is prepared and presented in the most suitable form.

WO 95/01977 discloses a magnesium salt of omeprazole with a specific degree of crystallinity making the claimed product especially suitable for pharmaceutical formulations; this is also discussed in WO 95/01783.

An efficient process for the manufacture of a magnesium salt of omeprazole is described in WO 97/41114. This process comprises mixing and reacting omeprazole with a weak base and a magnesium source and optionally the reaction takes place in the presence of an organic solvent. After the reaction is completed, the product is preferably crystallised from the filtrate.

Other processes related to the manufacture of alkaline salts of proton pump inhibitors are for instance disclosed in WO 94/27988, in which the preparation of the single enantiomers of omeprazole and alkaline salts thereof is described.

The present invention provides improvements over the prior art processes. It represents especially an improvement of the process described in WO 97/41114.

A pharmaceutical dosage form suitable for proton pump inhibitor compounds is for instance described in WO 96/01624. Said patent application describes preparation of small enteric coating layered pellets comprising the active substance. These enteric coating layered pellets are compressed into tablets. Preferably, the preparation of pellets containing the active substance is performed by spray layering the active substance onto seeds, such as for instance sugar spheres, and thereafter applying the enteric coating layer, optionally after a separating layer has first been applied to separate the active substance from the finally applied enteric coating layer.

Proton pump inhibitor compounds are acid susceptible and with respect to the stability properties of these compounds, it is obvious that an oral solid dosage form must be protected from contact with the acidic gastric juice and that active drug must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

The rate of release of the drug from a pharmaceutical dosage form can influence the total extent of absorption of such a drug into the general circulation. Omeprazole and related drugs as well as dosage forms comprising these drugs have been investigated (See for instance Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113–120). The marketing approval for these products specifies limits for the rate of release of the drug from the pharmaceutical dosage form.

SUMMARY OF THE INVENTION

The present invention provides an improved process for the preparation of an alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety and especially magnesium salts of substituted benzimidazole derivatives. The process results in a bulk product, which on addition of water, gives a suspension with a pH above a specified pH range. Said product is suitable for further processing into a pharmaceutical preparation. The release properties of such a pharmaceutical formulation comprising the new form of the active substance are improved. The claimed process provides especially a more suitable bulk drug product for pharmaceutical dosage forms, for intance a multiple unit tablet.

According to the improved process, an alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety is prepared, and the process comprises a final step wherein a base is added to a washing solvent to adjust the pH of the solution, which solution is used in the final wash of the product. Preferably, a magnesium salt of the substituted sulphinyl heterocycle compound is prepared according to WO 97/41114, hereby included by reference, by mixing and reacting the substituted sulfinyl heterocycle compound with a weak base, preferably an amine or ammonia, and a magnesium source, such as an organic or inorganic magnesium salt or a combination of such salts. Thereafter the crystallised and isolated magnesium salt product is washed with a basic aqueous solvent mixture.

The process may also be used to prepare other salts of substituted sulphinyl heterocycles containing an imidazole moiety, for instance slightly soluble or less soluble salts, preferably a multivalent salt such as a calcium salt, by the use of a calcium source or any other suitable source of that cation. Slightly soluble or less soluble salts are defined in compliance with the European Pharmacopiea (Edition 3) under the heading "General notice".

The present invention also provides an improved process for the preparation of a pharmaceutical dosage form by

spray layering of the active substance onto seeds, such as for instance sugar spheres. The active substance is preferably an acid susceptible drug selected from an alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety. The active substance is suspended in an aqueous solution of a macromolecular binding agent. The obtained suspension should have a pH not significantly lower than that of a saturated water solution of the pure drug substance.

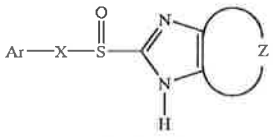
In one preferred embodiment, the claimed process relates to a process for the manufacturing of dosage forms comprising magnesium salts of substituted benzimidazole derivatives. More specifically, the process is related to the preparation of spray layered spheres with omeprazole magnesium in a water solution of a binding agent. The prepared pellets are covered by a separating layer and an enteric coating layer and filled into a capsule, or mixed with tablet excipients and compressed into a tableted multiple unit dosage form. Preferably, a tablet comprising a multiple of enteric coating layered units of omeprazole magnesium is prepared.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the result from testing the rate of release of omeprazole from sugar spheres spray layered with a suspension of omeprazole magnesium as prepared according to Example 2. Three graphs refer to pellets prepared according to the present invention and two graphs refer to reference pellets.

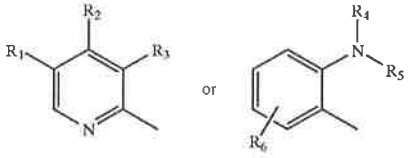
DETAILED DESCRIPTION OF THE INVENTION

According to one aspect, the present invention provides a novel method of preparing a slightly soluble or less soluble alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety with the following formula I



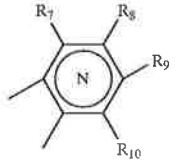
I

wherein Ar is



or

Z is



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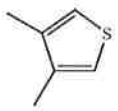

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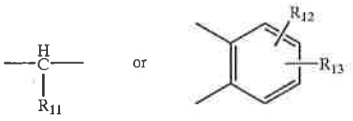


wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R_7–R_{10}optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6 is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_7–R_{10} are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_7–R_{10} form ring structures which may be further substituted;

R_{11} is hydrogen or forms an alkylene chain together with R_3 and

R_{12} and R_{13} are the same or different and selected from hydrogen, halogen or alkyl,

and wherein alkyl groups, alkoxy groups and moieties thereof may be branched and straight C_1–C_9-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl,

which process comprises the step of reacting the substituted sulphinyl heterocycle of Formula I with a source of the cation in the presence of a base. The process is characterised by a washing step in which the prepared alkaline salt of the substituted sulphinyl compound is washed with a basic aqueous solvent mixture. Such a preferred basic aqueous solvent mixture comprises for instance sodium hydroxide or ammonia, and preferably a solvent mixture comprising an alcohol, sodium hydroxide and water is used. The obtained bulk drug substance will, in an aqueous suspension of the substituted sulphinyl heterocycle of Formula I, have a pH equal to or above that of a saturated water solution of the pure alkaline salt of the substituted sulphinyl compound prepared.

In general, the present invention is applicable for the manufacturing of a slightly soluble or a less soluble alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety. The invention is exemplified with the manufacturing of omeprazole magnesium salt.

Preferably, the magnesium salt of omeprazole is prepared by reacting omeprazole with a magnesium source in the presence of a weak base as described in W097/41114, and the crystallised and isolated magnesium salt of omeprazole is washed with a basic aqueous solvent mixture.

One purpose of the present invention is to secure a pH not significantly lower than that of a saturated water solution of the pure compound when the manufactured bulk drug substance is suspended in water. Preferably, a suspension of omeprazole magnesium should have a pH of 9.5 or above in a 10% (w/w) suspension of the bulk substance. To obtain a suitable pH (as measured in a 10% suspension), a small amount of a base is added to increase the pH of the wash

solution in order keep the pH of the bulk drug substance, in water, at a value not significantly lower than that of a saturated water solution of the pure compound. As an example, pKa for omeprazole magnesium is 8.8, and theoretically the pH of a saturated solution of omeprazole magnesium in water is about 9.6 at room temperature.

A suitable non-volatile base to be added to the wash solution is sodium hydroxide which is added in an amount of not exceeding 0.1% (w/w) of the solid omeprazole magnesium and preferably not more than approximately 0.02%. Ammonia is another suitable base for the claimed process.

According to a second aspect, the invention provides an improved method of preparing a pharmaceutical dosage form comprising the step of spray layering the active substance suspended in an aqueous solution of a binding agent onto seeds, preferably sugar spheres. A suspension of the active substance in water, preferably 10–50 % (w/w), is mixed with a binding agent, and optionally wet-milled. The pH of the suspension is controlled and adjusted before spray layering onto sugar spheres in a fluid bed. In the following example, a 25% suspension of omeprazole magnesium is prepared. The pH of the suspension is controlled and/or adjusted to a value not significantly lower than that of a saturated water solution of pure omeprazole magnesium by addition of a base. Suitable bases are for instance sodium hydroxide and ammonia, which are added in an amount needed to raise the pH to a desirable value.

A saturated water solution of omeprazole magnesium has, theoretically, a pH of 9.6, and the aqueous suspension of omeprazole magnesium and binding agent should have a pH of 9.4 or above, and more preferably a pH of 9.5 or above.

One of the purposes of the present invention is to secure a pH not significantly lower than that of a saturated water solution of the pure compound when making the suspension for spray layering, i.e. when substance is suspended in an aqueous solution of the binding agent.

A suitable binding agent for the suspension of the active drug is a macromolecular agent, such as for instance celluloses such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose and carboxymethylcellulose sodium, polyvinyl pyrrolidone, gelatine, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. These binding agents can be used alone or in mixtures.

Furthermore, the suspension may comprise an alkaline reacting substance, in admixture with one or more pharmaceutically acceptable excipients. In addition to the binding agent, such excipients are for instance a disintegrating agent and/or a surface active ingredient.

The prepared spray layered units are enteric coated. Optionally the units are covered by a separating layer—before the enteric coating layer is applied—to separate the enteric coating layer from the active drug layer.

Suitable material and techniques for the seeds, enteric coating layering and the optional separating layer are known in the art. Preferred materials and techniques are for instance described in WO 96/01624, which is hereby included by reference.

Use of the Invention

Proton pump inhibitors are generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid secretory pathway. Thus, in a more general sense, it may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on non steroidal antiinflammatory drug (NSAID) therapy, in patients with non ulcer dyspepsia, in patients with symptomatic gastric-oesophageal reflux disease, and in patients with gastrinomas. It may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these, as well as in the treatment or prophylaxis of inflammatory conditions in mammals, including man.

Prepared dosage forms comprising a drug substance prepared according to the invention are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of other conditions higher doses than average will be used.

Preferably, a dose of the proton pump inhibitor, for instance 1–500 mg is administered once a day. Suitable doses comprise for instance about 5–100 mg of the substance, and more preferably 5–80 mg. The dosage form may be administered together with other suitable drugs, such as antibacterial compound(s), NSAID(s), motility stimulating agents, and/or antacids. The dosage form may alternatively be in the form of a tableted effervescent multiple unit dosage form.

The invention is further described and discussed in the following by examples. The intention of the examples is not to limiting the scope of the invention which scope is defined by the enclosed claims.

Results and Discussion

It is beneficial for the pharmaceutical processing that the bulk drug substance suspended in water will produce a pH in the suspension which is not significantly lower than that of a saturated water solution of the pure compound. For instance, a suspension of omeprazole magnesium should have a pH of about 9.6.

The invention is illustrated by Example 1 and Reference Example A describing dissolution rate from pharmaceutical dosage forms comprising sugar spheres that are spray layered with an aqueous suspension of omeprazole magnesium. As the results show, a pH significantly lower than that of a saturated water solution of pure omeprazole magnesium in the washing step of the manufacturing process of the bulk drug substance may cause a low dissolution rate of omeprazole magnesium from the prepared pellets (Reference example A). These results can be compared with a formulation comprising pellets prepared from omeprazole magnesium with a pH not significantly lower than that of a saturated water solution of pure omeprazole magnesium in the washing step of the manufacturing process of the bulk drug substance (Example 1). The mechanism behind this lowering of the dissolution rate from the pharmaceutical dosage form, might depend on co-precipitation of small amounts of the non-ionized and less soluble forms of the substance (in this case non-salt forms of omeprazole) at the surface of the dried material. Such possible precipitation of omeprazole, non-salt form, will not disturb the dissolution rate from the pharmaceutical dosage form, if the pH in the aqueous suspension prepared from omeprazole magnesium

and used for spray layering onto seeds is not significantly lower than that of a saturated water solution of pure omeprazole magnesium.

Furthermore, the invention is illustrated by Example 2 and Reference Example B. The prepared pellets were tested in USP dissolution apparatus with respect to release rate of omeprazole in phosphate buffer solution, pH 6.8; ionic strength I=0.16; temp 37° C.; stirring rate 100 rpm. The release of omeprazole was followed by spectrophotometric determination (302 nm) and the results are presented in FIG. 1.

The graphs show that the release of omeprazole can be increased by adjusting the pH to a value not significantly lower than that of a saturated water solution of the pure compound.

EXAMPLE 1

Examples of dissolution rate from pharmaceutical dosage forms manufactured from different batches of omeprazole magnesium prepared in accordance with the present invention.

Preparation

Multiple unit tablets comprising enteric coating layered pellets of omeprazole magnesium were prepared in accordance with the description in WO 96/01623, see Example 2. Omeprazole magnesium was prepared in accordance with WO 97/41114, and the omeprazole magnesium was washed with a basic aqueous solvent mixture (methanol/water) containing a small amount of sodium hydroxide corresponding to 0.02% w/w of the omeprazole magnesium substance. The prepared omeprazole magnesium was used in the manufacturing of multiple unit tablets.

Analysis

The pH-value of a water suspension (10% w/w) of omeprazole magnesium was measured (table I, column II), and the dissolution from manufactured tableted dosage forms of the respective batch of omeprazole magnesium was determined (table I, column III). The amount of omeprazole released within 30 minutes in a buffer solution was determined. The tablets were pre-exposed to 0.1 M hydrochloric acid at 37° C. for 2 hours.

TABLE I

pH-value of the aqueous suspension of omeprazole-Mg, and dissolution of omeprazole from a multiple unit tablet prepared from such omeprazole-Mg

Batch	pH of omeprazole -Mg (10% w/w in water)	Dissolution (%, 30 min; n = 6)
Susp. I*	9,7	94 (101–93)
Susp. II*	9,6	95 (93–97)
Susp. III**	10,3	95 (92–99)
Susp. IV**	10,1	93 (92–97)

*pH >9.5 no addition of base needed in the wash solution.
**Base added to the wash solution

Reference Example A

Examples of dissolution rate from pharmaceutical dosage forms manufactured from two different batches of omeprazole magnesium prepared without any addition of a base to the solvent used for washing of the omeprazole magnesium.

Preparation and Analysis

In accordance with Example 1, tableted dosage form were prepared from batches of omeprazole magnesium having a pH-value of a 10% w/w suspension in water significantly lower than that of a saturated solution of the pure compound and the corresponding dissolution rate from manufactured tablets was measured.

TABLE A

pH-value of the aqueous suspension of omeprazole-Mg, and dissolution of omeprazole from a multiple unit tablet prepared from such omeprazole-Mg

Batch	pH of omeprazole -Mg (10% w/w in water)	Dissolution (%, 30 min; n = 6)
Susp. A I	9.2	77 (81–73)
Susp. A II	9.2	71 (69–73)

The results from Example 1 and Reference Example A show that the addition of a base to the wash solution in the final washing step in the manufacturing of omeprazole magnesium, to increase the pH (resulting in an aqueous suspension of the omeprazole magnesium having a pH not significantly lower than that of a saturated water solution of pure omeprazole magnesium), has an influence on the dissolution rate from a tableted enteric coated pharmaceutical dosage form comprising said omeprazole magnesium.

EXAMPLE 2

Core material comprising omeprazole magnesium was prepared by spray layering a suspension of omeprazole magnesium onto sugar sphere seeds (0.25–0.35 mm) in a fluid bed apparatus.

Composition of the suspension:

omeprazole magnesium	25.0% (w/w)
hydroxypropyl methylcellulose	3.75% (w/w)
water	71.25% (w/w)

The pH of the suspension was controlled and adjusted by addition of a suitable amount of sodium hydroxide or ammonia to pH 9.6–9.7. Thereafter, 400–600 g of suspension was sprayed onto 100–150 g sugar spheres (0.25–0.35 mm). Three prepared experimental pellets were tested as described below, and results are shown in FIG. 1.

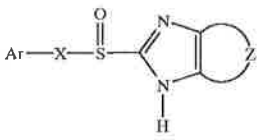
Reference Example B

Core material comprising omeprazole magnesium was prepared by spray layering a suspension of omeprazole magnesium onto sugar sphere seeds (0.25–0.35 mm) in a fluid bed apparatus as described in Example 2. The suspension of omeprazole magnesium had a pH value of 8.7 in both experiments. The prepared pellets were tested as described below, and the results are shown in FIG. 1.

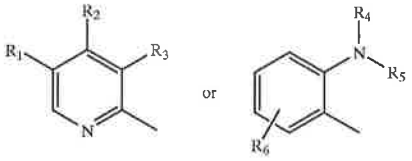
The prepared pellets were tested in USP Dissolution Apparatus No 2 (paddle) with respect to release rate of omeprazole in phosphate buffer solution pH 6.8; ionic strength 0.16; temperature 37° C.; stirring rate 100 rpm. The release of omeprazole was followed by spectrophotometric determination (302 nm).

What is claimed is:

1. A process for the manufacturing of slightly soluble or less soluble alkaline salts of substituted sulphinyl heterocycles containing an imidazole moiety with Formula I in the form of a racemate, one of the single enantiomers or an enantiomeric enriched form,



wherein
Ar is



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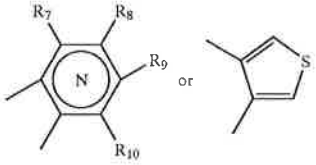
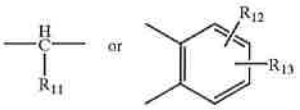


and X is



wherein
N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R_7–R_{10} optionally may be exchanged for a nitrogen atom without any substituents;
R_1, R_2 and R_3 are the same or different and selected from the group consisting of hydrogen, alkyl, alkylthio, alkoxy, alkoxy substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy;
R_4 and R_5 are the same or different and selected from the group consisting of hydrogen, alkyl and aralkyl;
R_6 is selected from the group consisting of hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;
R_7–R_{10} are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, and trifluoroalkyl, or adjacent groups R_7–R_{10} form ring structures which may be further substituted;
R_{11} is hydrogen or forms an alkylene chain together with R_3 and
R_{12} and R_{13} are the same or different and selected from the group consisting of hydrogen, halogen and alkyl,
and wherein alkyl groups, alkoxy groups and moieties thereof may be branched and straight C_1–C_9-chains or comprise cyclic alkyl groups, which process comprises the step of reacting the substituted sulphinyl heterocycle of Formula I with a source of the cation in the presence of a base, and a washing step in which the prepared alkaline salt of the substituted sulphinyl compound is washed with a basic aqueous solvent mixture.

2. The process according to claim 1, wherein the slightly soluble or less soluble alkaline salt of Formula I is a magnesium salt of the substituted sulphinyl heterocycle containing an imidazole moiety with Formula I.

3. The process according to claim 1, wherein the pH of the basic aqueous solvent mixture is adjusted by addition of a base to a pH resulting in a bulk product, that in an aqueous suspension of the substituted sulphinyl heterocycle, having a pH of not more than 0.2 pH-units lower than that of a saturated water solution of the pure alkaline salt of the substituted sulphinyl compound.

4. The process according to claim 3, wherein the base is sodium hydroxide or ammonia.

5. The process according to claim 1, wherein a magnesium salt of omeprazole is prepared.

6. The process according to claim 5, wherein the base added to the wash solution is sodium hydroxide in an amount not exceeding 0.1% (w/w) of the solid omeprazole magnesium.

7. The process according to claim 5, wherein the base added to the wash solution is sodium hydroxide in an amount of not exceeding 0.02% (w/w) of the solid omeprazole magnesium.

8. The process according to claim 1, wherein a magnesium salt of the (S)-omeprazole is prepared.

9. A pharmaceutical dosage form comprising a drug substance prepared according to any of claims 1–8.

10. A method of treatment of gastrointestinal diseases comprising the administration to a patient in the need thereof of a pharmaceutical dosage form comprising a drug substance prepared according to any of claims 1–8.

11. A process for the manufacture of a pharmaceutical dosage form comprising as active substance a compound manufactured according to any of claims 1–8,the process comprising the step of spray layering the active substance in the form of a suspension of the substance in a water solution of a binding agent onto seeds, wherein the pH of the aqueous suspension of the active substance is adjusted to a pH of not more than 0.2 pH-units lower than that of a saturated water solution of the pure alkaline salt of the substituted sulphinyl compound.

12. The process according to claim 11, wherein the suspension of the active substance is wet-milled to a micronised suspension.

13. The process according to claim 11, wherein the pH is adjusted by addition of a base.

14. the process according to claim 13, wherein the base is sodium hydroxide or ammonia.

15. The process according to claim 11, wherein the active substance is a magnesium salt of omeprazole.

16. The process according to claim 11, wherein the active substance is a magnesium salt of (S)-omeprazole.

17. A pharmaceutical dosage form prepared according to claim 11.

18. A method of treatment of gastrointestinal diseases comprising the administration to a patient in the need thereof of a pharmaceutical dosage according to claim 11.

* * * * *

EXHIBIT D

US006428810B1

(12) **United States Patent**
Bergstrand et al.

(10) **Patent No.: US 6,428,810 B1**
(45) **Date of Patent: Aug. 6, 2002**

(54) **PHARMACEUTICAL FORMULATION COMPRISING OMEPRAZOLE**

(75) Inventors: **Pontus Bergstrand**, Gothenburg; **Peter Wang**, Mölndal, both of (SE)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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§ 371 (c)(1),
(2), (4) Date: **Feb. 4, 2000**

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PCT Pub. Date: **May 18, 2000**

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(52) **U.S. Cl.** **424/480**; 424/464; 424/468; 424/472; 424/474

(58) **Field of Search** 424/464, 465, 424/467, 468, 469, 470, 480, 489; 514/960, 965

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Primary Examiner—Thurman K. Page
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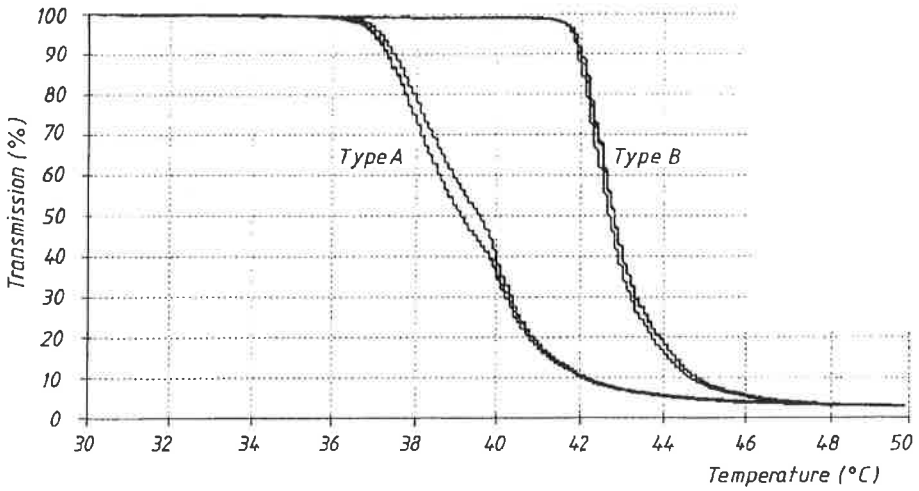
(57) **ABSTRACT**

An enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, one of the single enantiomers of omeprazole and an alkaline salt of one of the single enantiomers of omeprazole, wherein the formulation comprises a core material that comprises the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with a pharmaceutically acceptable excipient, such as for instance a binding agent, and on said core material a separating layer and an enteric coating layer. A hydroxypropyl cellulose (HPC) with a specific cloud point is used in the manufacture of the claimed pharmaceutical formulations. Furthermore, the application describes the processes for their preparation and the use of the claimed formulations in medicine.

22 Claims, 4 Drawing Sheets



Cloud point determinations of the two different qualities of HPC named Type A and Type B (according to Example 3).

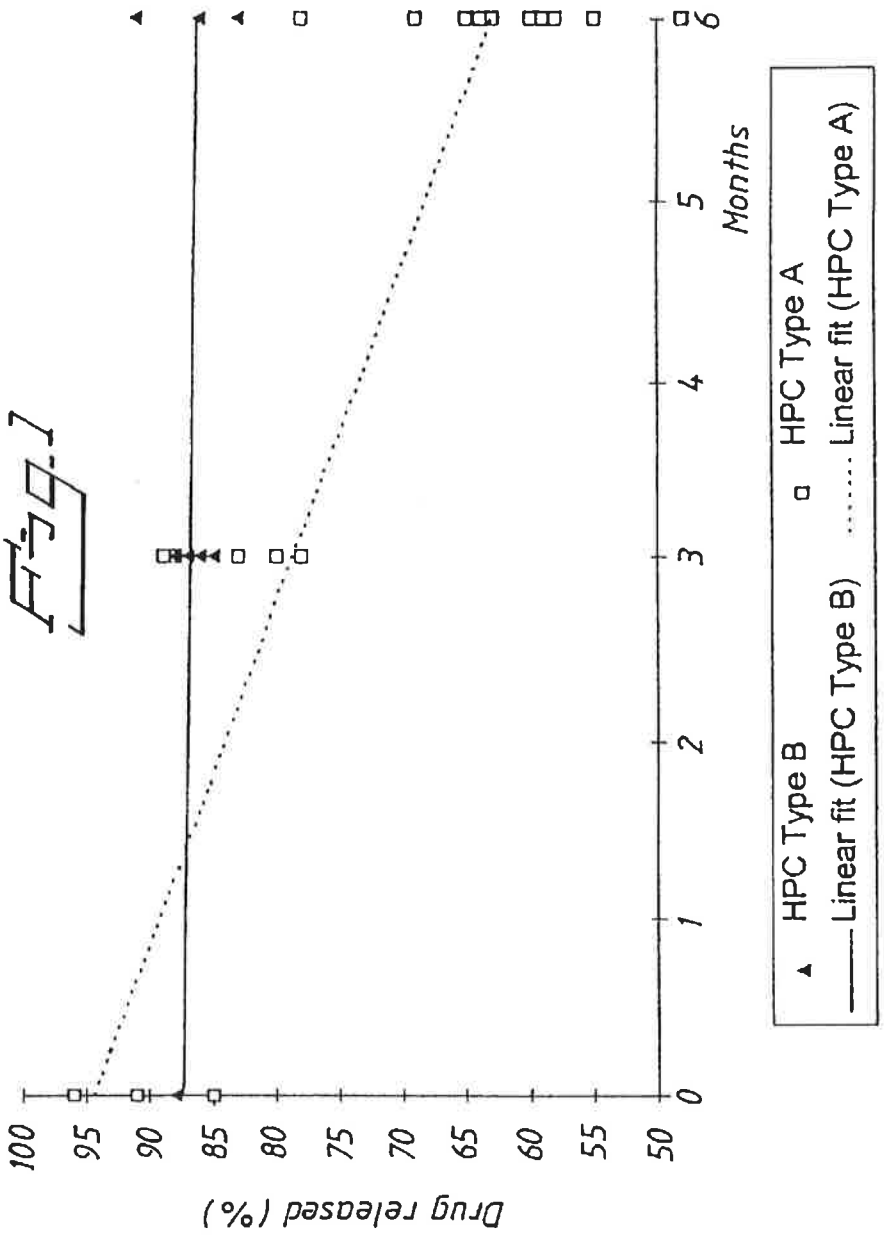


Figure 1. Drug released, after pre-exposure 2 hours to 0.1 M HCl and 30 minutes in buffer pH 6.8, from tablets containing HPC Type A and HPC Type B in the separating layer of enteric coated pellets (according to Example 2).

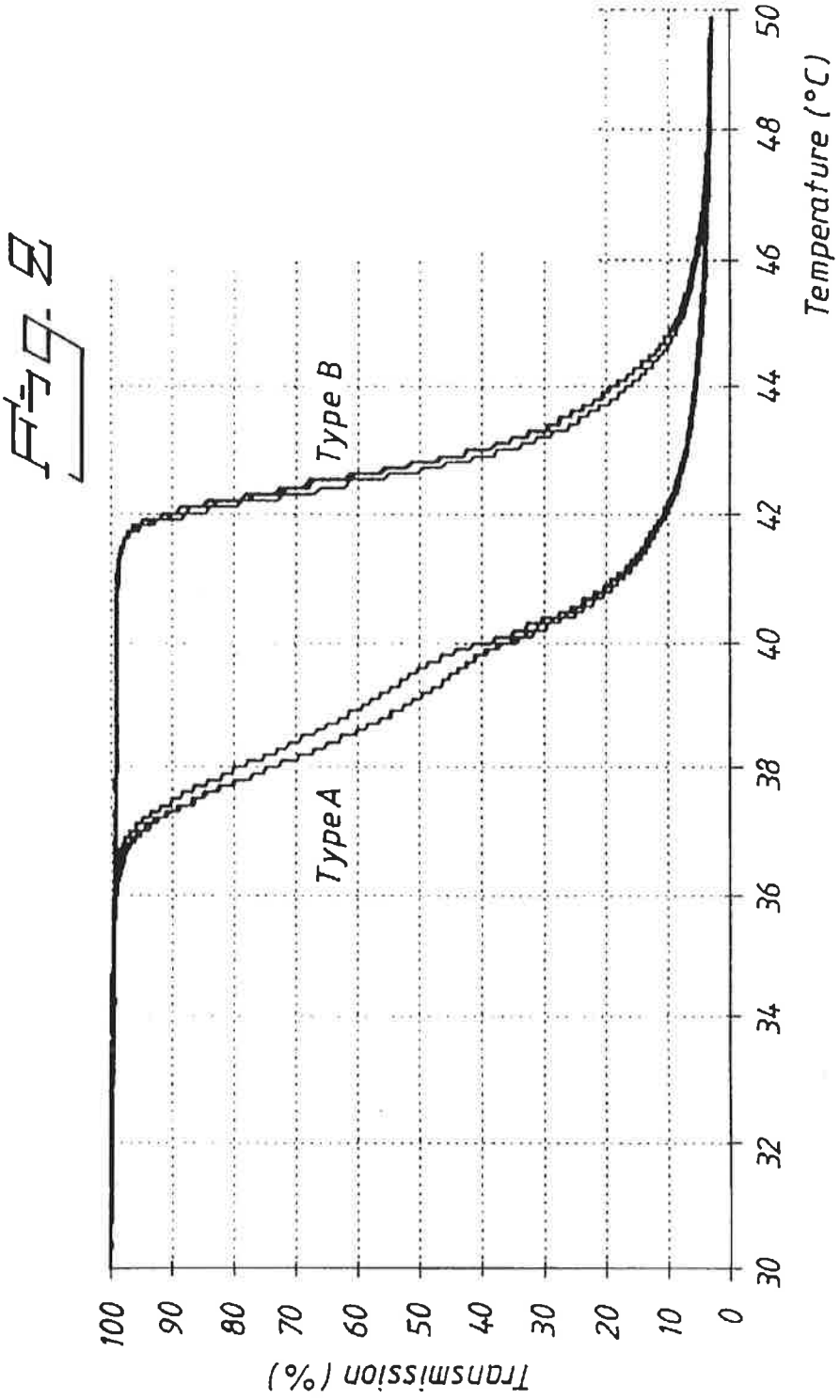


Figure 2. Cloud point determinations of the two different qualities of HPC named Type A and Type B (according to Example 3).

Fig. 3a

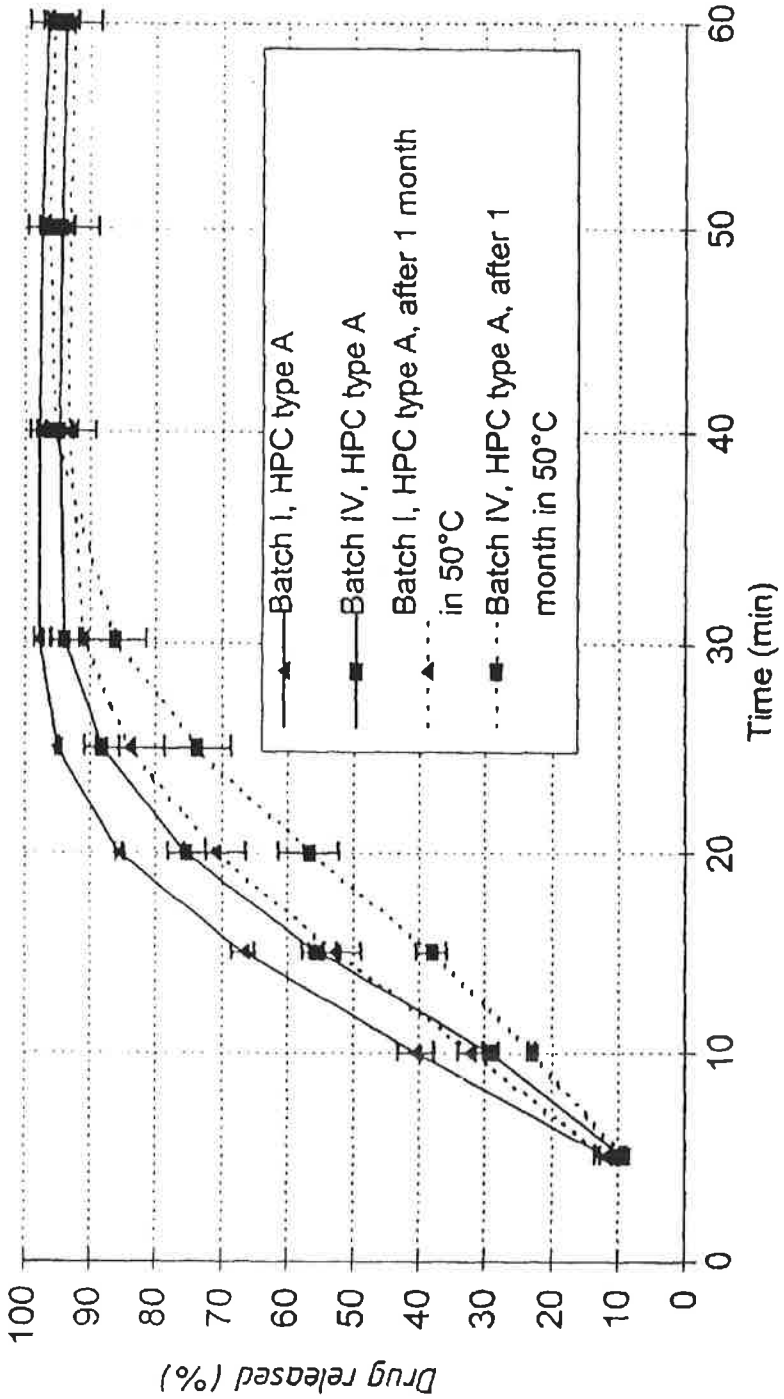


Figure 3a). Release of omeprazole from formulations containing HPC type A (according to Example 1) in separating layer of enteric coated pellets, before and after storage.

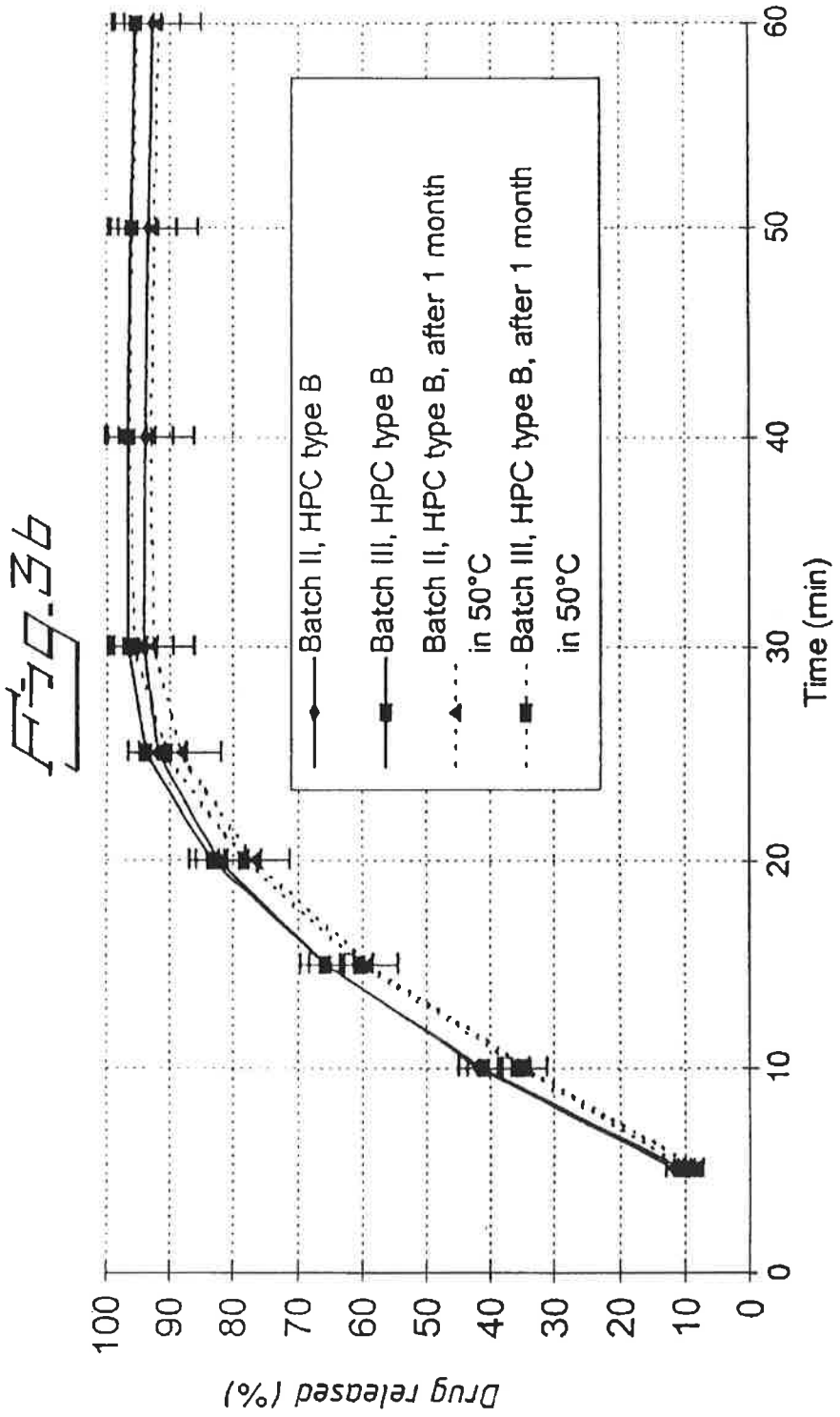


Figure 3b). Release of omeprazole from formulations containing HPC type B (according to Example 1) in separating layer of enteric coated pellets, before and after storage.

PHARMACEUTICAL FORMULATION COMPRISING OMEPRAZOLE

FIELD OF THE INVENTION

The present invention relates to an oral pharmaceutical formulation comprising the acid labile H^+, K^+-ATPase inhibitor omeprazole, an alkaline salt of omeprazole, one of the single enantiomers thereof or an alkaline salt of one of the single enantiomers of omeprazole. In the following these compounds are referred to as omeprazole. The formulation is in the form of a multiple unit dosage form that comprises enteric coating layered units of omeprazole. More specifically, the units comprise a core material that comprises omeprazole optionally in admixture with an alkaline reacting substance, and in admixture with one or more pharmaceutically acceptable excipients such as a binding agent, a filling agent and/or a disintegrating agent. Furthermore, each unit comprises a separating layer to separate the enteric coating layer from the core material. The separating layer comprises a specific quality of hydroxypropyl cellulose (HPC), and optionally pharmaceutical excipients. More specifically, the HPC quality is defined by having a specific cloud point.

Furthermore, the present invention refers to the use of the specific quality of HPC in the manufacture of a pharmaceutical formulation comprising omeprazole, and the use of such a pharmaceutical formulation in medicine.

BACKGROUND OF THE INVENTION

Omeprazole, an alkaline salt thereof, the single enantiomers of omeprazole and an alkaline salt of the single enantiomers of omeprazole, all compounds hereinafter referred to as omeprazole, are used in the treatment of gastric acid related diseases. Omeprazole and pharmaceutically acceptable salts thereof are described in EP 5129, and some specific alkaline salts of omeprazole are described in EP 124 495 and W095/01977. Certain salts of the single enantiomers of omeprazole and their preparations are described in WO94/27988.

Omeprazole is generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid secretory pathway. Thus, in a more general sense, it may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with non ulcer dyspepsia, in patients with symptomatic gastro-oesophageal reflux disease, and in patients with gastrinomas. It may also be used in a patient in intensive care situations, in a patient with acute upper gastrointestinal bleeding, pre-and post-operatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these, as well as in the treatment or prophylaxis of inflammatory conditions in mammals, including man.

Omeprazole is, however, susceptible to degradation or transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The chemical stability of omeprazole is also affected by moisture, heat, and organic solvents and to some degree by light.

Due to the chemical stability properties of omeprazole, it is obvious that an oral solid dosage form comprising omeprazole must be protected from contact with the acidic gastric juice. Omeprazole must also be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical oral dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. For instance, EP 247 983 describes enteric coated formulations of omeprazole. Such as formulation contains omeprazole in the form of a core unit containing omeprazole together with an alkaline salt or containing an alkaline salt of omeprazole optionally together with an alkaline salt, the core unit is layered with a separating layer and an enteric coating layer. In WO 96/01623 a multiple unit tableted dosage formulation comprising omeprazole is described.

The oral formulations described in EP 247 983 and the tablet formulations described in WO 96/01623 are examples of enteric coating layered formulations that comprise or optionally comprise a separating layer to separate the acidic enteric coating material from omeprazole being an acid susceptible substance. HPC may be used in a layer that separates the core material from the enteric coating layer in the described formulations. All ingredients, including HPC qualities, used in a pharmaceutical preparation must fulfil strict criteria, such as for instance requirements defined in pharmacopoeial monographs.

The rate of release of omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole into the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113–120). Therefore the limits for rate of release of the omeprazole from the pharmaceutical formulation are stated in the marketing approval for the products. The release of omeprazole is affected both by the chemical stability of the active substance and the release stability of the pharmaceutical formulation. If the formulation is unstable with respect to the release rate, the drug will have a non-accepted storage time, i.e. the expiration period for the product will be too short.

It has now surprisingly been found that different batches of HPC, which fulfil all pharmacopoeial requirements, used as material for the separating layer in a pharmaceutical formulation comprising omeprazole, may result in different release rate over time. Thus, the storage period for the pharmaceutical formulation may not be acceptable. One parameter of interest for the HPC's influence on the release stability is its water solubility.

The aqueous solubility of HPC decreases with increasing temperature due to polymer phase separation. This is observed as a clouding of the polymer solution when the temperature is increased. Cloud point is the temperature at which this polymer phase separation occurs. Cloud point is determined by measuring the light transmission through the polymer solution. The light transmission of a specific system where the polymer is dissolved, that is a transparent polymer solution without clouding, is defined as light transmission 100%. In this patent application cloud point is defined as the temperature where the light transmission of a specific system is 96% when a commercial instrument from Mettler is used. For other cloud point systems and instruments another light transmisson may be specified for each system.

One problem that can be avoided by the new formulation and use of a specific quality of HPC, is that the storage period for the dosage form can be extended and guarantied. From an economical aspect it is advantageous to specify and check the HPC quality thereby keeping a long expire date of the dosage form.

OUTLINE OF THE INVENTION

It has now been found that a quality of HPC with a cloud point of not less than 38° C. determined as the temperature where the light transmission of a specified system is 96% measured by a Mettler FP90/FP 81C instrument is desirable in an enteric coating layered pharmaceutical formulation comprising omeprazole. Preferably, the HPC should have a cloud point of not less than 40° C., and more preferably not less than 41° C. When another instrument is used for determination, the cloud point may be specified in other terms. An upper limit for the cloud point is not critical and therefore there is no need to specify that.

The HPC is used as a constituent of a separating layer separating the core material comprising omeprazole from the enteric coating layer. The HPC quality defined in the present patent application is desirable in fulfilling the criteria on release rate stability and to be suitable for oral administration forms comprising omeprazole.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. **1** shows two graphs representing two different dosage forms based on two qualities of HPC named Type A and Type B. The graphs show released omeprazole from the dosage forms after 3 months and 6 months storage at accelerated conditions at 40° C. and 75% relative humidity. The two HPC qualities are used as a constituent of the separating layer described in Example 2 below. With a separating layer comprising HPC Type A the release rate of omeprazole over time has decreased. With the HPC Type B the release rate of omeprazole over time is almost the same as for a freshly produced product.

FIG. **2** shows two graphs representing two different qualities of HPC named Type A and Type B. The graphs show cloud point determinations for the two HPC qualities used as a constituent of the separating layer described in Examples 1–3 below.

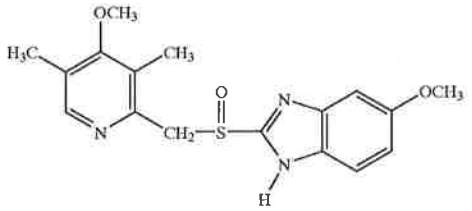
FIG. **3***a*) and FIG. **3***b*) show graphs representing two different dosage forms based on two qualities of HPC named Type A and Type B. FIG. **3***a*) shows released omeprazole from dosage forms comprising HPC type A, i.e. a reference. FIG. **3***b*) shows released omeprazole from dosage forms comprising HPC type B, i.e. according to the invention. The two HPC qualities are used as a constituent of the separating layer described in Example 1 below.

DETAILED DESCRIPTION OF THE INVENTION

Core Materials.

Omeprazole with formula Ia, is preferably formulated into an oral composition in the form of a pharmaceutically acceptable salt, such as an alkaline salt selected from the group of the Mg^{2+}, Ca^{2+}, Na^{+} and K^{+} salts, more preferably the Mg salt. Omeprazole may also be used in the form of one of the single enantiomers of omeprazole or an alkaline salt of one of the single enantiomers of omeprazole, especially an alkaline salt of the (−)-enantiomer of omeprazole, and more preferably the Mg^{2+} salt of the (−)-enantiomer of omeprazole.

(Ia)



The core material for the individually enteric coating layered pellets can be composed and formulated according to different principles, such as described in EP 247 983 and WO 96/01623 hereby incorporated by reference. For instance, omeprazole is mixed with one or more pharmaceutical constituents to obtain preferred handling and processing properties and also to obtain a suitable concentration of omeprazole in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

Preferably, omeprazole, optionally after mixing with an alkaline compound, is mixed with suitable constituents including a binding agent and formulated into a core material. Said core materials may be produced by extrusion/spheronization, balling or compression and by utilizing different process equipment. The formulated core materials may have a size of less than approximately 2 mm. The manufactured core materials can be layered further with additional ingredients, optionally comprising active substance, and/or be used for further processing.

Alternatively, inert seeds layered with active substance (the active substance is optionally mixed with alkaline compounds) can be used as the core material for the further processing. The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-parcils and other materials, alone or in mixtures.

Before the seeds are layered, for instance by using granulating or spray coating/layering equipment, omeprazole is mixed with a binding agent and optionally further components. Such further components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, microcrystalline cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants, such as for instance sodium lauryl sulphate.

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate co-precipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $Mg_6Al_2(OH)_{16}CO_3.4H_2O$,

$MgO.Al_2O_3$. $2SiO_2.nH_2O$ or similar compounds; organic ph-buffering substances such as trihydroxy methyl amino methane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Separating Layer(s)

The core material containing omeprazole must, according to EP 247 983, be separated from the enteric coating polymer(s) containing free carboxyl groups, which may otherwise cause degradation/discolouration of omeprazole during the coating process or during storage.

According to the present invention, the separating layer comprises a specific quality of HPC. This specific quality of HPC should preferably have a cloud point of at least 38° C. determined by a Mettler instrument. The cloud point is determined in a mixed disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3. The mixed solution used for the cloud point determination has a pH of 6.75–6.85. The concentration of HPC in the mixed solution is 1.0% (w/w) for the Mettler instrument. For more detailed information on the composition of the mixed solution, see below in the experimental section. Preferably, the HPC has a low viscosity, such as for instance below 400 mpas in a 5% (w/w) water solution at 25° C.

Alternatively, the quality of HPC may be determined by a method that correlates with the method described above, e.g. NIR spectrophotometry.

Additives such as plasticizers, colorants, pigments, fillers, anti-tacking, buffering agents, and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc, and other additives may also be included in the separating layer(s).

Enteric Coating Layer(s)

One or more enteric coating layers are applied onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in a suitable organic solvent. As enteric coating layer polymers one or more, separately or in combination, of the following polymers can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s). For environmental reasons, an aqueous coating process may be preferred. In such aqueous processes methacrylic acid copolymers are most preferred.

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain desirable mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers. The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s). Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate, methylmethacrylate), anti-tacking and anti-foaming agents may also be included in the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acidic susceptible active substance.

To protect the acidic susceptible active substance, the enteric coating layer(s) preferably constitute(s) a thickness of at least approximately 10 μm. The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

The pellets or units covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipment such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the layering process.

Final Dosage Form.

The prepared pellets may be filled in hard gelatine capsules or compressed with suitable tablet excipients into a tableted multiple unit formulation, and the latter is preferred. Final dosage forms may also include but is not restricted to effervescent tablets, and combinations of omeprazole with other active ingredients, such as for instance antibacterial substances, NSAID(s), motility stimulating agents or antacids.

Experimental Section.

EXAMPLE 1

Test of Omeprazole Multiple Unit Tablets, in which the Pellets are Layered with Different Types of HPC Used as a Constituent of the Separation Layer (Laboratory Scale).

Omeprazole tablets with the following composition were prepared according to the description in WO 96/01623. Sugar spheres were spray layered in a fluidized bed with an aqueous suspension of omeprazole magnesium salt and HPMC. The prepared pellets were layered with a separating layer and thereafter enteric coated. Enteric coated pellets were mixed with tablets excipients and compressed into a multiple unit tablet.

The composition of the tested omeprazole tablets (20 mg strenght) was as follows.

NAME OF INGREDIENT	FORMULA (mg/tablet)
Omeprazole magnesium	20,6
Glyceryl monostearate	1,4
Hydroxypropylcellulose	4,8
Hydroxypropyl metylcellulose	4,6
Magnesium stearate	0,7
Methacrylic acid copolymer type C	27
Microcrystalline cellulose	220
Polysorbate 89	0,1
Polyvinylpyrrolidone crosslinked	4,6
Sodium stearyl fumarate	0,5
Sugar spheres	22
Talc	8,3
Triethyl citrate	8,2

Omeprazole multiple unit tablets prepared with a separating layer on the pellets which separating layer comprises HPC, of either quality i.e type A or type B. HPC of the two types fulfill all requirements in the PhEur as well as the USP. However, the HPC of the two types differ with respect to some physical/chemical characteristics, e.g. cloud point.

The prepared tablets were tested according to the description below. The tablets, i.e. the pellets, were prepared from the same batch of omeprazole magnesium, and with the same enteric coating material. The release of omeprazole was tested on stored tablets after 0 month, and 6 months

storage. The amount of released omeprazole within 30 minutes in a buffer solution was determined.

The tablets were pre-exposed to hydrochloric acid at 37° C. for 2 hours. Thereafter the drug release in buffer solution pH 6.8 at 30 minutes was determined by liquid chromatography. The buffer solution pH 6.8 was a mixture of disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3, pH should be between 6.75 and 6.85. The hydrochloric acid 0.1 M was prepared by dissolving 213 ml of conc. HCl in water and added with water to 25 000 ml. The disodium hydrogen phosphate solution 0.086 M was prepared by dissolving 382 g $Na_2HPO_4.2H_2O$ in water and dilute to 25 000 ml with water.

The stability testing was performed on (20 mg strength) tablets packed in plastic bottles with desiccant (the tablets were not covered by a tablet coat).

Results are shown in FIG. **3***a*) and FIG. **3***b*). FIG. **3***a*) shows results with the HPC quality type A, i.e. a reference, and FIG. **3***b*) shows results with HPC type B, i.e. according to the instant invention.

EXAMPLE 2

Release of Omeprazole from Tablets Comprising Different Types of HPC as a Constituent of the Separating Layer

Pilot scale batches (using HPC of type A: 6 batches, and type B: 2 batches) were manufactured in order to confirm the improvement found during the laboratory testing in Example 1. Results from stability studies are shown in FIG. **1**.

The comparison clearly indicates improved release rate stability for tablets containing HPC of type B relative to that of type A.

General compositions for omeprazole tablets (20 mg strength):

NAME OF INGREDIENT	FORMULA (mg/tablet)
Omeprazole magnesium	20.6
Colour iron oxide reddish-brown	0.3
Glyceryl monostearate	1.4
Hydroxypropylcellulose	4.8
Hydroxypropyl metylcellulose	15
Magnesium stearate	0.7
Methacrylic acid copolymer type C	27
Microcrystalline cellulose	220
Paraffin	0.2
Polyethylene glycol 6000	2.5
Polysorbate 80	0.1
Polyvinylpyrrolidone crosslinked	4.6
Sodium stearyl fumarate	0.5
Sugar spheres	22
Talc	8.3
Titanium dioxide	2.2
Triethyl citrate	8.2

The tablets were manufactured as described in example 1, with the additional step of a tablet coat comprising HPMC, PEG 6 000, and pigment.

EXAMPLE 3

Cloud Point Determinations

Omeprazole tablets were manufactured in laboratory scale as described in example 1.

Cloud point determinations of the HPC types in the Mettler instrument was conducted in the following way. The cloud point of the HPC types was determined in a mixed phosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3. The mixed solution used for the cloud point determination had a pH of 6.75–6.85. The concentration of HPC in the mixed solution was 1.0% (w/w). It is essential for the specificity of the cloud point determination that this system is used in the chosen instrument. The Mettler instrument comprises the following parts: Mettler FP90 Central processor, FP81C Measuring unit and ME-18572 boiling point tubes. A temperature range of 30.0 to 50.0° C. was used and a heating rate of 1.0° C./min. The cloud point is defined as the temperature where the light transmission is 96%.

The results are shown in FIG. **2**.

What is claimed is:

1. An enteric coated oral pharmaceutical formulation comprising:

(a) a core material which comprises an active ingredient selected from the group consisting of omeprazole, an alkaline salt of omeprazole, one of the single enantiomers of omeprazole and an alkaline salt of one of the single enantiomers of omeprazole;

(b) a separating layer; and

(c) an enteric coating layer,

wherein the separating layer comprises a hydroxypropyl cellulose (HPC) with a cloud point of at least 38° C., and

wherein the light transmission at cloud point of a system comprising the HPC dissolved in a concentration of 1.0% (w/w) in a mixed solution of disodium hydrogen phosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3 at a pH of 6.75–6.85 is 96%.

2. The formulation according to claim **1**, wherein the HPC has a cloud point of at least 40° C.

3. The formulation according to clam **1**, wherein the HPC has a cloud point of at least 41° C.

4. The formulation according to claim **1**, wherein the enteric coating layer comprises a methacrylic acid copolymer.

5. The formulation according to claim **1**, wherein the HPC has a low viscosity.

6. The formulation according to claim **1**, wherein the active ingredient is omeprazole.

7. The formulation according to claim **1**, wherein the active ingredient is a magnesium salt of omeprazole.

8. The formulation according to claim **1**, wherein the active ingredient is a magnesium salt of the (−)-enantiomer of omeprazole.

9. The formulation according to claim **1**, wherein the core material further comprises an alkaline reacting compound.

10. The formulation according to claim **1** or **9**, wherein the core material further comprises a pharmaceutically acceptable excipient selected from the group consisting of binding agents, fillers, lubricants, disintegrating agents, surfactants and mixtures thereof.

11. A method for the treatment of gastrointestinal diseases in mammals comprising administering to a host in need thereof a therapeutically effective amount of the pharmaceutical formulation according to any one of claims **2–8** or **1**.

12. A process for the manufacture of an enteric coated oral pharmaceutical formulation according to claim **1**, comprising the steps:

(a) forming the core material comprising the active ingredient;

(b) applying the separating layer onto the core; and

(c) applying the enteric coating layer onto the core coated with the separating layer.

13. The process according to claim **12**, wherein an alkaline reacting compound is mixed with the active ingredient to form the core material.

14. The process according to claim **12** or **13**, wherein a pharmaceutically acceptable excipient selected from the group consisting of binding agents, fillers, lubricants, disintegrating agents, surfactants and mixtures thereof is added to form the core material.

15. The process according to claim **12**, wherein an alkaline reacting compound is mixed with the active ingredient and a binding agent to form the core material.

16. The process according to claim **12**, wherein the HPC has a cloud point of at least 40° C.

17. The process according to claim **12**, wherein the HPC has a cloud point of at least 41° C.

18. The process according to claim **12**, wherein the enteric coating layer comprises a methacrylic acid copolymer.

19. The process according to claim **12**, wherein the HPC has a low viscosity.

20. The process according to claim **12**, wherein the active ingredient is omeprazole.

21. The process according to claim **12**, wherein the active ingredient is a magnesium salt of omeprazole.

22. The process according to claim **12**, wherein the active ingredient is a magnesium salt of the (−)-enantiomer of omeprazole.

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